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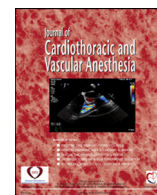
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## Review Article

## New Developments in Hemodynamic Monitoring

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Hemodynamic monitoring is an essential part of the perioperative management of the cardiovascular patient. It helps to detect hemodynamic alterations, diagnose their underlying causes, and optimize oxygen delivery to the tissues. Furthermore, hemodynamic monitoring is necessary to evaluate the adequacy of therapeutic interventions such as volume expansion or vasoactive medications. Recent developments include the move from static to dynamic variables to assess conditions such as cardiac preload and fluid responsiveness and the transition to less-invasive or even noninvasive monitoring techniques, at least in the perioperative setting. This review describes the available techniques that currently are being used in the care of the cardiovascular patient and discusses their strengths and limitations. Even though the thermodilution method remains the gold standard for measuring cardiac output (CO), the use of the pulmonary artery catheter has declined over the last decades, even in the setting of cardiovascular anesthesia. The transpulmonary thermodilution method, in addition to accurately measuring CO, provides the user with some additional helpful variables, of which extravascular lung water is probably the most interesting. Less-invasive monitoring techniques use, for example, pulse contour analysis to originate flow-derived variables such as stroke volume and CO from the arterial pressure signal, or they may measure the velocity-time integral in the descending aorta to estimate the stroke volume, using, for example, the esophageal Doppler. Completely noninvasive methods such as the volume clamp method use finger cuffs to reconstruct the arterial pressure waveform, from which stroke volume and CO are calculated. All of these less-invasive CO monitoring devices have percentage errors around 40% compared with reference methods (thermodilution), meaning that the values are not interchangeable.

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THE GOALS OF precise, personalized hemodynamic monitoring—improving outcomes and patient safety—are the reasons new and better technologies are instituted after they are developed. Clinicians believe that these technologies will improve management of the patient under anesthesia and in the intensive care unit by providing accurate information that can be used to optimize care, provide early diagnosis, and provide feedback that the therapies instituted are improving the perfusion of vital organs and the microcirculation such that the physiological environment is maintained optimally. However, accurate and predictive hemodynamic assessment may be difficult. Anticipating when deterioration is imminent is challenging because the etiology may be multifactorial and involve

volume status; myocardial function; vascular tone; and patient resilience, which is still very hard to assess. These monitors are tested in clinical trials with the anticipation that they will provide accuracy (truth) and precision (repeatability), but sometimes they are “black boxes” as far as the user is concerned.<sup>1</sup> However, this is the cost of innovation, and industry and scientists must be encouraged to continue to pursue novel developments but test the outcomes clinically.

## The Move From Static to Dynamic Measurements

In the last century, monitoring has developed from initially pressure focused and noninvasive (eg, finger on the pulse and listening to heart and Korotkoff sounds) to invasive (eg, central venous pressure, arterial pressure, and pulmonary artery pressure). However, invasive technology is associated with complications such as infection and perforation. In recent

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years, the focus has been on trying to develop noninvasive technology without losing significant accuracy and precision, avoiding the complications of invasive monitors, and analyzing flow and response to fluid therapy. In 1968 Prys-Roberts commented on an observation made by Jarisch in 1928 that flow is so much more difficult to measure than pressure but adequate flow is vital for cellular well-being.<sup>2</sup> Waveform analysis of the pulse contour is used to calculate stroke volume and cardiac output (CO), and the effect of respiratory variation on this waveform has been used to estimate fluid responsiveness or where the patient's volume status is placed on the Frank-Starling curve.

The goal of patient-centered hemodynamic monitoring is to make correct therapeutic decisions and optimize the cardiovascular system in the patient undergoing surgery or intensive care treatment. Perioperative acute kidney injury (AKI) is associated with increased morbidity and mortality and until recently has been underdiagnosed. It is estimated that between 22% and 57% of patients admitted to the intensive care unit will develop AKI during their admission<sup>3</sup> and that current AKI classification underestimates long-term mortality.<sup>4</sup> Early diagnosis has been helped by the development of new biomarkers<sup>5</sup> so that effective preventive and therapeutic measures can be developed. The avoidance of hypotension and renal hypoperfusion and the optimization of volume status are the goals for preventing renal ischemia. Goal-directed fluid therapy guided by dynamic variables such as the pleth variability index (PVI), pulse pressure variation (PPV) and stroke volume variation (SVV) has been developed to measure fluid responsiveness.<sup>6</sup> The PVI is a measure of the dynamic changes in the perfusion index that occur during 1 or more complete respiratory cycles and is measured using pulse oximetry. This respiratory variation in the pulse oximeter waveform is strongly related to changes in arterial pulse pressure, which is sensitive to changes in ventricular preload in mechanically ventilated patients and more recently has been shown to accurately predict fluid responsiveness.<sup>7-9</sup> The traditional methods of measuring cardiac preload still are used to predict volume responsiveness, but multiple studies have shown inaccuracy in these static variables, such as central venous pressure, pulmonary artery occlusion pressure, left ventricular end-diastolic dimensions, early- or late-diastolic wave ratio, and B-type natriuretic peptide concentration, in demonstrating volume responders from nonresponders.<sup>10-14</sup> Dynamic tests that challenge the Frank-Starling curve may predict fluid responsiveness but are limited if spontaneous ventilation is present or cardiac arrhythmias are occurring. However, a pulse pressure variation (PPV) or PVI >13% is highly predictive of fluid responsiveness in mechanically ventilated patients in sinus rhythm. Goal-directed fluid management using PVI has been demonstrated to reduce perioperative lactate levels compared with standard measures, including central venous pressure, blood pressure, and fluid challenge. The authors used a PVI threshold of 14% to infuse volume.<sup>15</sup>

Central venous pressure is a helpful indicator of cardiac preload, but not preload responsiveness, and depends on the shape of the Frank-Starling curve, as do all static markers of preload.

SVV and PPV are other minimally invasive or noninvasive dynamic variables that can be used to guide fluid management. These again are more accurate in mechanically ventilated patients in sinus rhythm. Arterial pulse pressure (systolic minus diastolic) is directly proportional to stroke volume. This PPV reflects the magnitude of respiratory changes in stroke volume and reflects the degree of preload responsiveness. This has been well-demonstrated in patients on mechanical ventilation with normal tidal volumes and sinus rhythm.<sup>16,17</sup>

### Transition to Minimally Invasive and Noninvasive Hemodynamic Monitoring Techniques

There undoubtedly has been a trend in recent years from more invasive hemodynamic monitoring tools and techniques (eg, pulmonary artery catheter [PAC] for measuring CO, mixed venous oxygen saturation, and pulmonary arterial pressures), to less-invasive techniques (eg, CO monitoring using arterial pressure waveform analysis or the esophageal Doppler), and even completely noninvasive techniques (eg, volume clamp using finger cuffs, bioimpedance and bioreactance, carbon dioxide (CO<sub>2</sub>)-rebreathing, and pulse wave transit time). This trend became possible through the technical development of innovative devices that have penetrated the market with variable success. The core question to be asked is whether less invasiveness also is accompanied by less accuracy,<sup>18</sup> which would limit the use of these devices markedly.

Although the pulmonary thermodilution method using the PAC remains the gold standard for measuring CO, the use of these techniques has declined over the last decades.<sup>19,20</sup> Reasons for this include the lack of benefit to treatment algorithms based on PAC measurements.<sup>21-23</sup> This also holds true for the population of high-risk patients undergoing cardiac surgery, for which the PAC still is widely used.<sup>24</sup>

That is slightly different from the transpulmonary thermodilution (TPTD) method, which, although invasive, only necessitates the insertion of a central venous line and an arterial thermistor catheter.<sup>25</sup> CO measured using this method might be considered interchangeable with that obtained by the gold standard (intermittent thermodilution with the PAC).<sup>26</sup> In addition to measuring CO with intermittent thermodilution, TPTD systems also provide continuous CO measurements by pulse contour analysis (PCA), which can be calibrated by measurements of bolus thermodilution, increasing their accuracy. In addition to CO, TPTD systems provide the user with additional hemodynamic measurements, including SVV and PPV, for assessing fluid responsiveness, global end-diastolic volume for estimating cardiac preload, extravascular lung water for quantifying pulmonary edema, pulmonary vascular permeability index for evaluating capillary leakage, and cardiac function index and ejection fraction as indicators of systolic pump function of the heart. These measurements allow for a complete hemodynamic evaluation of the patient experiencing shock, therefore TPTD is recommended for evaluating acute circulatory failure that does not respond to initial therapy or that is associated with acute respiratory distress syndrome.<sup>27</sup> Of these multiple variables, extravascular lung water is probably the most interesting because

it clearly correlates with severity categories of acute respiratory distress syndrome<sup>28</sup> and with mortality in critically ill patients.<sup>29</sup>

Amongst the less-invasive hemodynamic monitoring technologies, those based on PCA are the most broadly used. PCA basically transfers a pressure signal (the arterial pressure waveform) into a flow signal. There are several monitors on the market, each of which uses its own proprietary algorithm for analyzing the pulse contour. The most common one uses the FloTrac sensor (Edwards Lifesciences, Irvine, CA), which can be connected to any arterial catheter on the patient side and to either the Vigileo, EV1000, or Hemosphere as the monitor (all Edwards Lifesciences). The system derives stroke volume from the pulse pressure of the arterial pulse wave after correcting for the compliance and the resistance of the vasculature. The accuracy of the CO measurements has been questioned, particularly in patients with low vascular resistance, which has led to multiple software updates of the algorithm to account for these problems. The results of the accuracy of CO data were summarized for the first 3 software generations, showing percentage error deviations from reference CO measurements (mostly PAC or TPTD) ranging from 13% to as high as 75%, depending on the setting.<sup>30</sup> After publication of that review, a fourth-generation software was released and tested, concluding that the accuracy of CO values measured with this version has improved greatly compared with previous versions but still did not reach a clinically sufficient level (ie, a percentage error <30%).<sup>31–33</sup>

Another uncalibrated PCA system for monitoring CO is the ProAQT/PulsioFlex system (Pulsion-Geringe, Feldkirchen, Germany). It essentially uses the PCA-based algorithm of the PiCCO system (Pulsion-Geringe), however, without the possibility of external validation by TPTD. Data regarding the accuracy of this device are scarce but indicate that the ProAQT/PulsioFlex did not reliably estimate the absolute values of CO.<sup>34</sup> In addition to the accuracy of an absolute CO value, one might be also interested as to whether a monitoring device can track changes in CO, such as after volume expansion or pharmacological interventions. In this respect, both methods (ie, FloTrac and ProAQT) perform better and reliably track these changes.

Additional PCA-based CO monitoring systems include the LiDCOrapid (LiDCO, London, UK) and the pressure recording analytical method. Taken in summary, these minimally invasive PCA-based technologies have a moderate accuracy with a percentage error of  $41.3\% \pm 2.7\%$ .<sup>35</sup>

The esophageal Doppler (Cardio Q; Deltex Medical, Chichester, UK) measures blood flow in the descending aorta via a flexible Doppler probe introduced into the esophagus of anesthetized patients. Unlike transesophageal echocardiography, the transducer is directed toward the descending aorta to measure the stroke distance (ie, the velocity-time integral), which then is used to estimate the stroke volume.<sup>36</sup> The mean percentage error for this device was  $42.1\% \pm 9.9\%$ .<sup>35</sup>

Completely noninvasive hemodynamic monitoring methods come into play when not even the placement of an arterial line is considered necessary for patient care. These methods can be used to measure not only blood pressure continuously, but also

CO and dynamic preload variables.<sup>37</sup> The first group of noninvasive CO technologies is based on principles similar to the PCA methods previously described, with the only difference being the arterial pulse wave is obtained noninvasively.<sup>27</sup> The so-called volume clamp method uses finger cuffs and relies on photoplethysmography to keep the finger blood volume constant,<sup>38</sup> as first described in 1967 by the Czech physiologist Penaz. This way, the arterial pressure waveform can be reconstructed and CO can be calculated using the CO-Trek algorithm.<sup>39</sup> This method was incorporated in the Nexfin monitor (BMEYE, Amsterdam, Netherlands), which was adopted by Edwards Lifesciences in 2014 and merchandised under the name ClearSight. Because the technology has not changed, results obtained with the Nexfin also are applicable to the ClearSight system. Studies examining CO estimates by this method show a percentage error ranging from 24% to 58% (average 44%) compared with TPTD.<sup>40</sup> A similar technology is used in the CNAP monitor (CNSystems Medizintechnik AG, Graz, Austria), which also has shown acceptable agreement with reference CO obtained using TPTD.<sup>41</sup> In a systematic review of noninvasive CO monitoring devices, the noninvasive PCA showed a pooled percentage error of 45%.<sup>42</sup>

Other noninvasive CO monitors that are not based on PCA include bioreactance and bioimpedance,<sup>43</sup> partial CO<sub>2</sub>-rebreathing,<sup>44</sup> and pulse wave transit time. These methods recently have been described in detail.<sup>38,45,46</sup> In a recent meta-analysis, percentage errors for these CO monitoring devices were 42% for bioimpedance and bioreactance, 40% for CO<sub>2</sub>-rebreathing, and 62% for pulse wave transit time.<sup>42</sup>

As stated by a recent expert panel, noninvasive hemodynamic monitors increasingly are being used in the perioperative setting and with further technological improvements have the potential to become the hemodynamic monitoring of the future. This is different for the intensive care unit setting for patients experiencing shock, who necessitate arterial catheterization (eg, for blood sampling), and when abnormal vasomotor states such as sepsis or hepatic failure limit the accuracy of CO measurements.<sup>27</sup> However, it must be mentioned that the choice of a monitoring technique based on patient factors (eg, comorbidities and risk of surgery) and the setting can be modified if the patient's condition deteriorates (step up approach) or improves (step down) with regard to invasiveness and continuity of measurements.<sup>47</sup> In the near future, technical developments such as miniaturized and wearable sensors and wireless monitoring will contribute to the widespread use of noninvasive hemodynamic monitoring technologies.<sup>48,49</sup>

## Introduction of Artificial Intelligence to Predict Hemodynamic Changes

Artificial intelligence, machine learning, big data, and predictive analytics are key words that infiltrate modern medicine just as they do in any other technology-associated field of science. These words describe a process of incorporating large amounts of disparate data into a unified algorithm, which then is used to predict and solve a clinical problem. Examples of their application include image processing of radiographic

images,<sup>50</sup> analysis of whole-slide pathology images,<sup>51</sup> fully automated echocardiogram interpretation,<sup>52</sup> and text analysis of clinical notes.<sup>53</sup> The October 2018 issue of the journal *Anesthesiology* was dedicated to this topic, summarizing the first applications to the specialty of anesthesiology and what practicing clinicians need to know.<sup>54</sup> It states that machine learning is a discipline within computer science used to analyze large data sets (big data) and develop predictive models (or algorithms). It is used to analyze and model complex associations and relationship patterns between multiple variables that are otherwise occult to the human eye, are more simplistic vision interfaces such as patient data monitors, or go beyond the limits of human understanding. The authors also depicted the information flow within the predictive modeling process for machine learning, using data sets for developing, training, and testing the model, which finally is validated by an external data set.<sup>54</sup> The issue also contains 2 examples of applying machine-learning–based predictive analytics to predict hypotension, a clinically relevant problem that is associated with unfavorable outcome such as myocardial and renal injury<sup>55,56</sup> and even increased mortality.<sup>57,58</sup>

In the first article, Hatib et al. describe the development of an algorithm to predict an upcoming hypotensive event (defined as a mean arterial pressure <65 mmHg).<sup>59</sup> The mathematical algorithm called the hypotension prediction index (HPI) was developed by learning from almost 13,000 past hypotensive events and more than 12,000 nonhypotensive events, derived from large data sets of high-fidelity arterial waveforms from almost 1,700 patients. Each of the arterial waveforms were first separated into 5 phases (such as systolic and diastolic, upstroke and decay), from which more than 3,000 waveform features were identified. By combining these individual features, more than 2.6 million waveform features were obtained, which then were reduced by selection processes to 51 base features that were used for model training. Using the aforementioned approach, patient data were split into a training and cross-validation cohort and an internal validation cohort. In addition, prospective patient data from an academic hospital were used for external validation. The results showed that the HPI algorithm was able to predict hypotension with high sensitivity and specificity up to 15 minutes before the actual hypotensive event occurred and that it performed better than changes in mean arterial pressure did. These results have been confirmed by a recent observational study in 255 patients undergoing major surgery, which also showed that the HPI algorithm performed better in predicting an upcoming hypotensive event than any other commonly measured hemodynamic variable did.<sup>60</sup> The HPI thus may buy time to take measures before the hypotensive event actually occurs, which implies a change in current practice from reactive to proactive blood pressure management. However, it must be realized that not all hypotensive events are predictable by examining the arterial waveform changes before the hypotensive event. These events include sudden changes in blood pressure as induced by vascular clamping, bolus administration of anesthetics, or activation of neuraxial blocks, just to name a few.

In the second example, Kendale et al. used a similar approach to predict postinduction hypotension, defined as a mean arterial pressure <55 mmHg occurring within 10 minutes after induction of anesthesia.<sup>61</sup> The authors used data from more than 13,000 patients undergoing general anesthesia, again split into a training and test set, to compare the performance of different machine-learning models. They found that postinduction hypotension occurred in about 9% of patients and that the best prediction models included the use of a gradient boosting machine with an area under the receiver operating curve (AUC) of 0.76, which then was used for further testing. This was followed by the model using a different mean arterial pressure threshold of 65 mmHg with an AUC of 0.72, the model using the need for administration of vasopressors (AUC = 0.75) and the down-sampled training set (AUC = 0.76). The study showed that machine-learning models were feasible as a systematic approach to predict postinduction hypotension.

Additional successful examples of the use of machine-learning–based algorithms in the field of anesthesiology include the prediction of complications after surgery such as sepsis and AKI,<sup>62</sup> the prediction of mortality after cardiac surgery,<sup>63</sup> and the prediction of postoperative pain and associated resources consumption.<sup>64,65</sup> Also, in the intensive care unit setting, predictive analytics based on hemodynamic variables have been used to reduce the incidence of septic shock.<sup>66</sup>

In summary, even though artificial intelligence may not be an ideal approach for all tasks, it may offer solutions to a number of clinical problems and outcomes, which due to their complex nature, withstand the assault of sustained thinking and conventional approaches. It bears, however, the hazard of creating new black boxes when the algorithms lack transparency. Nevertheless, artificial intelligence has the potential to be incorporated into clinical decision support systems and to help clinicians adhere to practice guidelines at the bedside. However, data to support the beneficial effect of such approaches on patient outcome are lacking.

## Conclusions

New methods of hemodynamic monitoring have the potential to improve management of the cardiovascular patient during anesthesia and postoperative care because they provide accurate, precise, and repeatable measurements that can be used to detect hemodynamic alterations and their causes, optimize hemodynamic conditions such as oxygen delivery to the tissues, and provide feedback on the adequacy of therapeutic interventions. Recent developments include the move from static to dynamic variables to assess for conditions such as cardiac preload and fluid responsiveness and the transition to less-invasive monitoring techniques, at least in the perioperative setting. Future objectives include wearable sensors and wireless remote monitoring, broadening continuous vital sign monitoring to lower care units such as general hospital wards. Furthermore, the introduction of artificial intelligence and machine learning will, based on big data, allow for predictive analytics of hemodynamic problems before they actually occur.



## Conflicts of Interest

T.W.L. Scheeren received research grants and honoraria from Edwards Lifesciences (Irvine, CA) and Masimo Inc. (Irvine, CA) for consulting and lecturing and from Pulsion-Geringe (Feldkirchen, Germany) for lecturing. M.A.E. Ramsay received research grants from Masimo Inc.

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